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ORIGINAL ARTICLE

Longer survival with precision medicine in late-stage cancer patients☆

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Background: In a per-protocol analysis of molecularly profiled patients with treatment-refractory, end-stage cancer discussed at the National Molecular Tumor Board (NMTB), we aimed to assess the overall survival (OS) outcome of targeted treatment compared with no targeted treatment.

Materials and methods: Patients were prospectively included at a single oncological center. Whole exome and RNA sequencing (tumor-normal) were carried out, and cases were presented at the NMTB for discussion of targeted treatment. Treatment was available through a basket trial, by compassionate use or in early clinical trials.

Results: One hundred and ninety-six patients were included from 2020 to 2023. In all but three patients a driver variant was disclosed, while 42% had simultaneous affection of more than three oncogenic pathways. In 42% of patients a druggable target was identified but two-thirds did not receive the suggested treatment. The fraction of patients initiating treatment yearly rose from 8% to 22%. For patients treated ($N = 30$), the clinical benefit rate was 44% and median time on treatment was 3.5 months. Druggable targets were enriched in lung cancers, while patients receiving or not receiving targeted treatment had similar clinical characteristics. The median OS was longer for patients receiving targeted treatment (15 months), but similar for patients with no druggable target and suggested targeted treatment not initiated (5 and 6 months, respectively) ($P = 0.004$). In multivariate analysis, targeted treatment (hazard ratio 0.43, confidence interval 0.25-0.72), few metastatic sites, and adenocarcinoma histology were predictive of improved OS while alterations of the RTK/RAS pathway were prognostically unfavorable.

Conclusions: Tissue-agnostic targeted treatment based on molecular tumor profiling is possible in an increasing fraction of end-stage cancer patients. In those who receive targeted treatment, results strongly suggest a significant survival benefit.

Key words: precision medicine, prognosis, tissue agnostic, clinical trial, molecular pathway analysis

INTRODUCTION

Today, precision medicine in cancer as part of standard of care is mostly based on targeting molecular alterations in tumors of specific tissue types or anatomical sites of origin.[2] This is due to randomized studies reporting robust outcomes observed with specific targeted therapies in patients selected by tumor type, compared with nonselective treatments such as chemotherapy.[3] However, next-generation sequencing (NGS) of advanced cancers has demonstrated that genomic alterations do not belong to categories defined by the tumors' organ of origin.[4,5] Clinical trials have evolved, shifting from tumor-type-centered to gene-biomarker-directed with the goal to improve outcomes.[6-8] Furthermore, metastatic tumors harbor complex and individually unique genomic and immune landscapes.[9,10] Therefore, targeted treatment must be personalized, as each cancer's complex molecular and immune landscape differs from patient to patient. This paradigm shift is revolutionizing oncology.[9] Currently, the US Food and Drug Administration (FDA) has approved several tissue-agnostic indications in cancer that include treatments directed toward high microsatellite instability (MSI-H) or mismatch repair deficiency (dMMR), *RET* fusions, high tumor mutational burden (TMB-H), the variant $BRAF^{V600E}$, *NTRK* fusions, *FGFR1* rearrangements,[11] and *HER2* alterations,[12] and numerous molecular targets that are emerging.[13]

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Because of the poor outcome of standard treatment in late-stage cancer, it is imperative to develop new strategies to improve the survival rate for these patients in particular. The feasibility and challenges of precision medicine in treatment-refractory cancer patients using a histology-agnostic approach have been described in numerous prior reports.[14-17] In these patients it has been demonstrated that targeted treatment may induce tumor response or delay progression if a druggable target can be identified,[6] but the impact on patients' survival is rarely reported.[18] Long-term responders represent a minority,[6] and improved selection of patients who might benefit the most is greatly needed. In the present study, we describe the effects of treating actionable molecular variants in a prospective, single-institutional cohort of patients with treatment-refractory cancers with survival as primary outcome.

MATERIALS AND METHODS

Patients

All patients were prospectively included in the Proseq Cancer trial (NCT05695638) that aims to assess the value of precision medicine in patients with advanced and incurable malignancies at a single academic center. Additional inclusion criteria were age >18 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2, expected survival >3 months, and no serious comorbidities prohibiting oncological treatment. An interim intention-to-treat analysis of all patients with solid tumors included in the protocol in the first 2 years was previously published.[19] For this per-protocol analysis, we included only patients in whom a molecular profiling was carried out and subsequently discussed at the National Molecular Tumor Board (NMTB). Furthermore, the inclusion period was extended to 3 years, and the patients were required to have a follow-up period of at least 10 months, sufficient for analysis of survival outcome.

All clinical data were prospectively entered by investigators into a secure REDCap database[20] and further associated with genomic data through a custom-built solution.[21] Vital status and treatment data were updated by April 2024.

Molecular profiling

In the vast majority (83%) of cases, new biopsies were taken and used for genomic tumor analysis, whereas fresh frozen tissue from initial surgery was used in 25 central nervous system-tumor cases. The protocol for molecular tumor-tissue profiling by whole exome sequencing (WES) and RNA sequencing (RNAseq) with parallel sequencing of non-tumoral DNA in plasma as individual reference has been previously described.[19] In non-tumoral DNA, clinically relevant pathogenic variants were detected only in *BRCA1/2*, *ATM*, *MLH1*, *MSH2/3*, *PMS1/2*, *MLH3/6*, *PALB2*, and *RAD51C/D*. In the few cases where tumor biopsy was not feasible, DNA extracted from archival formalin-fixed paraffin-embedded tissue ($n = 7$) or plasma (circulating tumor DNA) ($n = 2$) was used for tumor profiling.[19] In these cases, RNAseq was not done.

Oncogenic pathway analysis was carried out retrospectively on the samples. The filtered somatic variants detected from the WES data were annotated using Funcotator from GATK version (4.5.0.0) with Funcotator data source v1.8.hg38.20230908s and converted to Mutation Annotation Format (MAF) files. Subsequently, the R Bioconductor package Maftools[22] was used to calculate the number of variants in each of the 10 oncogenic signaling pathways for each patient, as described by Sanchez-Vega et al.[23]

Pathology

Tumor biopsies taken in parallel to the biopsy for genomic analysis were examined by senior consultant pathologists. The specimens were diagnosed reporting percentage of vital tumor cells and histological subtype. Additional analyses included, in most cases, human epidermal growth factor receptor 2 (HER2) and MMR protein-expression assessed by immunohistochemistry (IHC). All previous pathological data on the cancer of the individual patient were recorded, including prior results of IHC, NGS of targeted tumor panels, and genetic tests of the germline.

National Molecular Tumor Board

Cases were presented at the weekly NMTB for discussion of targeted treatment. The board is led by the Phase 1 Unit at Rigshospitalet, Copenhagen, and participants include specialist oncologists, molecular biologists, bioinformaticians, clinical geneticists, and pathologists from all centers in Denmark involved in oncological precision medicine and early-phase trials of targeted drugs. Treatment was available locally through a multicenter basket trial[24] or by compassionate/off-label use, as well as patients could be referred to clinical trials at other centers. In this study, a 'druggable' target was defined pragmatically as a molecular target for which a matched treatment was available and feasible as determined by the NMTB in individual cases, based on clinical and molecular features. Treatment outside of clinical trials was recommended only if clinical data indicating benefit to patients were available from published reports.

ESMO Scale for Clinical Actionability of molecular Targets classification

We retrospectively assessed the current evidence for actionability according to the European Society for Medical Oncology Scale for Clinical Actionability of molecular Targets (ESCAT) classification of targeted treatments.[25] The scoring was done by two observers independently, without access to clinical outcome data. In cases of discrepancy, scoring was discussed and agreed upon.

Endpoints

The primary endpoint was overall survival (OS) from the date of NMTB for three subgroups: (i) patients with a druggable target who received a targeted treatment, (ii) patients with a druggable target who did not receive a targeted treatment, and (iii) patients with no druggable target. Secondary endpoints were the fraction of patients with a druggable target and the fraction of patients with a druggable target who received a targeted treatment per year of NMTB. For patients receiving a targeted treatment, time to treatment failure (TTF) and clinical benefit rate (CBR) were additional secondary endpoints. Response was assessed according to RECIST ver. 1.1[26] only in patients with measurable disease at baseline. CBR was defined as the fraction of patients obtaining complete response (CR), partial response (PR), or stable disease (SD) lasting >16 weeks.[27] Additional analyses were carried out to identify factors predicting absence of a druggable target and, in patients with druggable targets, factors predicting no targeted treatment.

Statistics

All statistical analyses were carried out using R version 4.2.0. Comparisons of tumor and clinical characteristics between groups were conducted using the Mann—Whitney *U* test for continuous variables, chi-square test for categorical variables with cell counts >5, and Fisher's exact test for categorical variables with cell counts ≤5. TTF and OS were evaluated using the Kaplan—Meier estimator, and results are given as medians and 95% confidence intervals (95% CIs). Follow-up was at least 10 months (median, 27 months) from the date of NMTB. No patients were lost to follow-up. OS was also evaluated applying Cox proportional hazards models. Firstly, univariate analyses were carried out for baseline characteristics to identify those significantly associated with OS. Secondly, a multivariate Cox regression analysis was carried out, including the significant characteristics. Results with a P value < 0.05 were considered statistically significant, without adjustment for multiple testing.

Ethics

All patients provided informed consent before enrollment in the trial allowing for biobanking, registration of clinical and laboratory data, and sharing of genomic data with the purpose of research, while fulfilling the Danish General Data Protection Regulation requirements. The trial was approved by the Ethics Committee of Northern Jutland, Denmark (N-20200018).

RESULTS

A total of 236 patients were prospectively included in the trial from June 2020 to May 2023, with 196 patients (83%) representing the per-protocol population.[1] In all but three patients, at least one oncogenic driver variant was found.

Baseline characteristics of the three specified patient subgroups are presented in Table 1 and compared by the absence or presence of a druggable molecular alteration and by targeted treatment being initiated or not initiated. With the notable exception that patients with lung cancer were significantly more likely to have a druggable target, clinical characteristics were similar among those with or without a druggable molecular alteration. Patients with an untreated druggable target exhibited similar clinical characteristics to those with a treated druggable target, although a non-significant trend for patients with fewer metastatic sites and in good ECOG PS being treated more often was observed. Targeted treatment was initiated more frequently in cases with rare histopathologic diagnoses. As shown in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2024.104089, the total number of oncogenic pathways affected was significantly associated with the occurrence of druggable targets, but individual affections of the NFR2, TGFβ2, or WNT pathways were not. Patients with tumors having the PIK3 oncogenic pathway affected were significantly less likely to initiate the suggested treatment.

A druggable target was identified at the NMTB for 83 patients representing 42% of the per-protocol population. Thirty patients initiated the suggested treatment (15% of the per-protocol population), while one patient remains on standard treatment. Hence, two-thirds of patients ($n = 52$) with potentially druggable targets did not receive the suggested treatment. The most frequent reasons were deteriorating performance status or early death in 27 patients, prior treatment against target in 11 patients, and suggested treatment not available in 10 patients (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2024.104089). At the time of NMTB, patients with untreated druggable targets received single-drug chemotherapy in 26 cases, two-drug chemotherapy in 14 cases, immune checkpoint inhibitors in 8 cases, and hormone or small-molecule inhibitors in 2 cases each,. Moreover, the line of palliative treatment was first in 5 cases, second in 20 cases, third in 13 cases, and fourth or more in 15 cases. Thirty-two patients (60.3%) did not receive further treatment lines.

The fraction of patients initiating a targeted treatment rose from 8% in the first year to 16% in the second year and 22% in the third year as well as the fraction of patients with a suggested druggable target rose from ∼38% in the first 2 years to 49% in the third year (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2024.104089).

Figure 1 shows the tumor primary site, histopathologic diagnoses, and molecular targets in the 83 patients with a potentially druggable target. The most common targets were TMB-H ($n = 20$) and *ERBB2* alterations ($n = 18$), including amplification ($n = 8$), pathogenic mutations ($n = 4$), and both ($n = 6$). Details of the patients treated are shown in Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.104089. In summary, 36 targeted treatments were given to 30 patients and included

Table 1. Clinical and tumor characteristics of 196 molecularly profiled end-stage cancer patients distributed according to groups with no druggable target, target present but untreated, and target present and treated

Variable	Stratum	A: No target (N = 113)	B: Untreated target (N = 53)	C: Treated target (N = 30)	P value A versus B + C	P value B versus C
Age in years	Median (min, max)	65 (30, 81)	63 (32, 79)	64.5 (18, 76)	0.97	0.56
Gender	Female	62 (55%)	31 (59%)	19 (63%)	0.55	0.84
	Male	51 (45%)	22 (42%)	11 (37%)		
Histology	AdC	73 (65%)	32 (60%)	20 (67%)	0.90	0.74
	SCC	10 (8.8%)	2 (3.8%)	2 (6.7%)	0.42	0.62
	Malignant glioma	18 (16%)	4 (7.5%)	2 (6.7%)	0.11	1.00
	Other[a]	12 (11%)	15 (28%)	6 (20%)	0.57	0.01
Primary site	Breast	12 (11%)	10 (19%)	4 (13%)	0.29	0.73
	Lung	9 (8.0%)	14 (26%)	7 (23%)	<0.001	0.96
	Ovaries	18 (16%)	3 (5.7%)	6 (20%)	0.42	0.10
	Brain	20 (18%)	4 (7.5%)	3 (10%)	0.10	1.00
	Prostate	13 (12%)	6 (11%)	4 (13%)	1.00	1.00
	Other[b]	41 (36%)	16 (30%)	6 (20%)	0.20	0.45
Time from diagnosis in years[c]	Median (min, max)	2.1 (0.06, 18)	2.2 (0.06, 22)	1.9 (0.20, 27)	0.55	0.89
Number of metastatic sites[d]	Median (min, max)	2 (0, 5)	2 (0, 5)	2 (0, 3)	0.64	0.20
Metastatic sites[e]	Liver	34 (30%)	21 (40%)	10 (33%)	0.36	0.74
	Lung	28 (25%)	15 (28%)	11 (37%)	0.39	0.59
	Bone	27 (24%)	18 (34%)	7 (23%)	0.42	0.44
	Distant lymph nodes	49 (43%)	28 (53%)	13 (43%)	0.49	0.55
ECOG PS	0	57 (50%)	19 (36%)	16 (53%)	0.43	0.09
	1	51 (45%)	28 (53%)	14 (47%)		
	2	5 (4.4%)	6 (11%)	0		
Number of prior systemic treatment regimens	Median (min, max)	3 (0, 10)	2 (0, 10)	2 (0, 9)	0.71	0.30
Prior high-dose radiotherapy	Yes	30 (27%)	9 (17%)	6 (20%)	0.22	0.96
	No	83 (73%)	44 (83%)	24 (80%)		
BMI	Median (min, max) (missing)	26 (18, 44) (2)	26 (18, 38)	26 (19, 52)	0.17	0.77
Smoking status	Never	40 (35%)	17 (32%)	11 (37%)	0.99	1.00
	Current/former	61 (54%)	28 (53%)	17 (57%)		
	Missing	12 (11%)	8 (15%)	2 (6.7%)		
Prior or concurrent other cancer	Yes	21 (19%)	10 (19%)	5 (17%)	1.00	1.00
	No	92 (81%)	43 (81%)	25 (83%)		
Germline variant	Yes	0	5 (9.4%)	4 (13%)	0.001	0.88
	No	110 (97%)	46 (87%)	25 (83%)		
	Undetermined	3 (2.7%)	2 (3.8%)	1 (3.3%)		

AdC, Adenocarcinoma; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NMTB, National Molecular Tumor Board; SCC, squamous-cell carcinoma.

[a]'Other histologies' include neuroendocrine carcinoma, basal cell carcinoma, mesothelioma, carcinosarcoma, atypical meningioma, and transitional cell carcinoma.

[b]'Other primary sites' include female genital tract excluding ovaries, esophagus-stomach, head-and-neck, skin, pancreas, and urinary tract.

[c]Time from first diagnosis of cancer to date of NMTB.

[d]The 31 patients with locally advanced disease are scored 0.

[e]Patients may have more than one metastatic site. Rarer metastatic sites are not shown or tested.

small-molecule inhibitors (SMIs) and immune checkpoint inhibitors (ICIs) (11 cases each), HER2-targeted drugs (10 cases), and poly-ADP-ribose-polymerase inhibitors (4 cases). Measurable disease at baseline was present for 33 of the treatments. Of these, one resulted in a CR, six in PR, and eight patients obtained SD >16 weeks resulting in a CBR of 45%. A comparison of TTF in treatment subgroups according to drug classes showed no clear differences (Figure 2). On reassessment, 23 treatments were ESCAT tier 1, 6 were tier 2, and 7 were tier 3. No significant differences among tiers according to TTF (P = 0.50) or OS (P = 0.20) were found. The median TTF was 3.5 months (95% CI 2.7-6.3 months) and one-third of patients were on treatment at 6 months (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2024.104089). Reasons for stopping treatment were PD in 20 cases, clinical progression in 8 cases, and toxicity in 2 cases (respectively, hypercalcemic crisis and severe fatigue), with both patients being treated with an fibroblast growth factor receptor inhibitor. We assessed the impact of numbers of metastatic sites on TTF of first targeted treatment, excluding patients with brain tumors. Differences were statistically insignificant (P = 0.20), but patients with long TTF were seemingly enriched in those with no distant metastases or a single metastatic site compared with multiple sites (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2024.104089).

In the survival analyses (Table 2), RTK/RAS pathway affection and ECOG PS 2 were poor prognostic factors, while targeted treatment, adeno- and squamous-cell carcinoma histology, breast primary, long interval from cancer diagnosis, and few metastatic sites were predictive of good prognosis. In multivariate analysis, targeted treatment, adenocarcinoma histology, number of metastatic sites, time from cancer diagnosis, and affection of the RTK/RAS

Figure 1. Tumor primary site (inner circle), histology (intermediate circle), and suggested druggable molecular target (outer circle) in 83 patients. Number of patients in each primary site category is shown in parenthesis. In patients who were not treated and had more than one druggable target, the one recommended for first targeted treatment is shown. In patients treated, all treated druggable targets are shown (see also Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2024.104089). '*HER2* alt' (alterations) include increased gene copy numbers, pathogenic mutations, and overexpression detected by IHC. '*FGFR* alt' includes pathogenic mutations and fusions. The diagnoses of 'other' include one case each of head-and-neck, uterine cervix and vaginal cancer.
AdC, adenocarcinoma; alt, alterations; amp, amplification; BCC, basal cell carcinoma; Ca NOS, carcinoma not otherwise specified; CaSa, carcinosarcoma; dMMR, mismatch repair deficient; GI tract, gastrointestinal tract; HRD, homologous recombination deficiency; IHC, immunohistochemistry; MM, malignant melanoma; MSI-H, microsatellite instability high; NEC, neuroendocrine carcinoma; SCC, squamous-cell carcinoma; TCC, transitional cell carcinoma; TMB-H, tumor mutational burden high.

pathway remained statistically significant. A multivariate analysis excluding brain tumors showed similar results (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2024.104089). TMB-H was observed in 19% of tumors, while affection of more than three oncogenic pathways was seen in 42% of cases, the most frequent being the RTK/RAS (61%) and P53 (59%) pathways. Individual genes affected in patients with alterations in the RTK/RAS pathway are shown in Figure 3. Stratified analysis showed that alteration of this pathway was highly predictive of poor survival in 128 patients with untreated or no druggable targets ($P < 0.001$), whereas no significant difference in survival was found in 28 patients treated with matched targeted therapy ($P = 0.60$).

The survival curves of patients distributed according to molecular and treatment characteristics are shown in

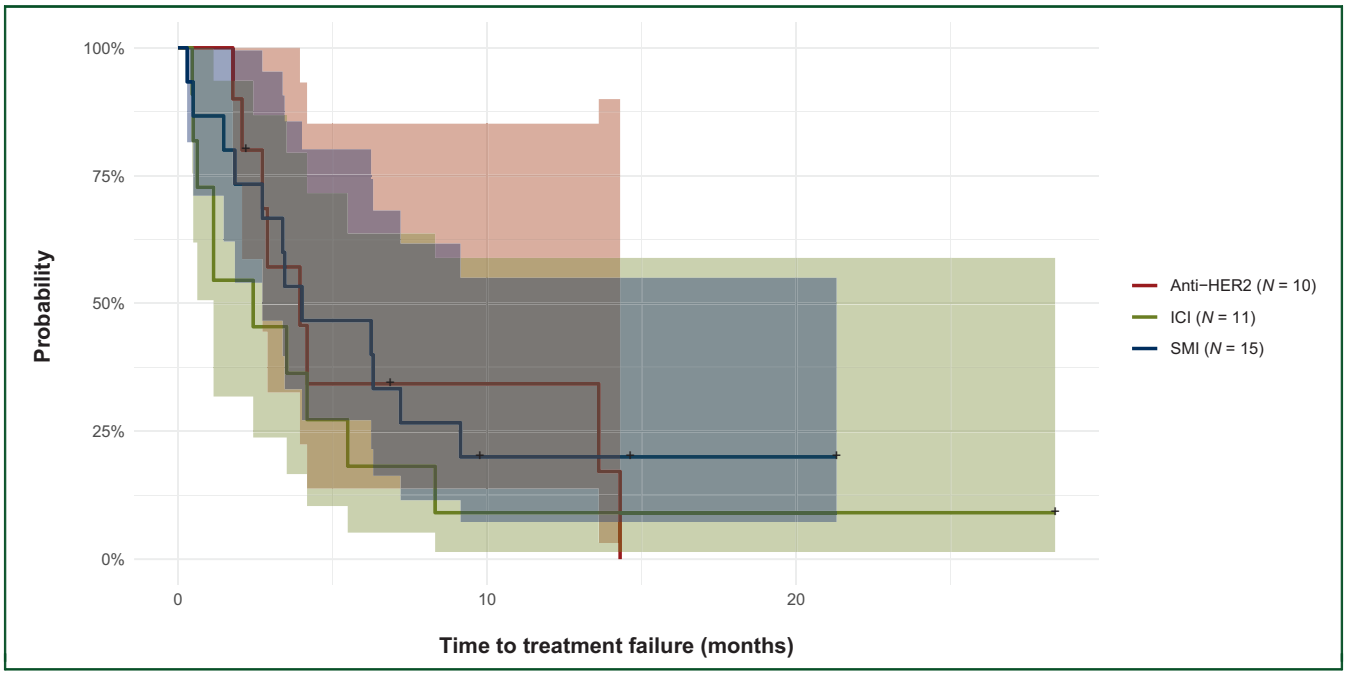

Figure 2. Time to treatment failure according to drug class of 36 molecular targeted treatments in 30 patients. Index date is the starting date of treatment. Six patients were censored (+), four being on-treatment and two pausing treatment without progression. SMI includes four patients treated with PARPi.
HER2, human epidermal growth factor receptor 2; ICI, immune check point inhibitor; PARPi, poly-ADP-ribose-polymerase inhibitor; SMI, small-molecule inhibitor.

Figure 4. The median OS from date of NMTB was ∼2.6 times longer for patients with a recommended targeted treatment initiated [15.7 months (95% CI 9.2 months-not reached)] as compared with patients not treated by targeted drugs ($P = 0.004$), but similar for patients with no druggable targets [6.5 months (95% CI 5.2-8.4 months)] and patients with a recommended targeted treatment not initiated [5.8 months (95% CI 4.6-8.8 months)].

DISCUSSION

In the present observational study, the main finding was a 2.6 times longer median survival of late-stage patients who had been treated with matched targeted agents compared with that of patients who were not offered such treatment, either due to lack of molecular target or lack of treatment initiation. In multivariate analysis, targeted treatment was the strongest independent predictor of improved survival. We also showed that the number of metastatic sites was a prognostic factor in accordance with findings in, e.g. triple-negative breast cancer[28] and non-small-cell lung cancer.[29] Plausible explanations are that this parameter may reflect both the tumor burden and aggressiveness, even in clinical stage IV disease. The OS results compare favorably with the few prior studies of tissue-agnostic precision medicine reporting on survival outcomes.[17,30,31] In an early status from the MD Anderson Cancer Center initiative, OS of patients with one molecular aberration was 11.4 months in the matched therapy cohort ($N = 143$) compared with 8.6 months in the unmatched cohort ($N = 236$) ($P = 0.04$).[32] In the IMPACT trial, the median OS was 9.3 months for 711 patients receiving matched therapy and 7.3 months for 2776 patients with alterations who did not receive matched therapy ($P < 0.0001$). In this large study, independent poor prognostic factors of the full cohort were ECOG PS > 1, liver metastases, elevated lactate dehydrogenase, PI3K/AKT/mTOR pathway alterations, and non-matched therapy.[33] Investigators of the PREDICT trial profiled 347 patients with solid advanced cancers. Eighty-seven of these were treated according to their genomic profile, but no difference in OS was observed.[34] Outcome results should, however, be interpreted in the light of recent developments of more efficient drugs including those directed against new targets.[11]

Assessment of overall clinical benefit of targeted treatment in heterogenous single-arm cohorts is not trivial.[35] In some clinical trials the progression-free survival (PFS) of prior untargeted treatment and PFS of targeted treatment are compared for each patient and a PFS ratio above 1.3 or 1.5 is interpreted as treatment benefit.[13] The PFS ratio may, however, be influenced by intrinsic differences in tumor behavior[36] and by selective inclusion of patients with limited effect of prior treatment. In the current and in many other trials, CBR—a composite of tumor response and delay of tumor progression—is used as a measure of effect.[37] The inclusion of delayed tumor progression may, however, overestimate efficacy for biologically indolent tumors and the association of CBR with OS benefit has not been firmly established.[38] In our cohort, we found a CBR of 45% of targeted treatment, which compares favorably with most reports, including a CBR of 33% found in the first 500 patients treated in the DRUP study[39] and 37% in 132 patients in the Mi-ONCOSEQ study,[40] but was almost similar to that of 40% in 145 patients reported in a recent publication from

Table 2. Analysis of factors predicting survival in 196 molecularly profiled end-stage cancer patients

Variable	Stratum	Number	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Target and treatment subgroup	No target	113	Ref		Ref	
	Treated targeted	30	0.46 (0.28-0.74)	0.002	0.43 (0.26-0.73)	0.001
	Untreated target	53	1.01 (0.72-1.43)	0.94	0.94 (0.64-1.39)	0.73
Age (years)		196	1.00 (0.99-1.01)	0.98		
Gender	Female	112	Ref			
	Male	84	1.17 (0.86-1.60)	0.31		
Histology	Other[a]	33	Ref		Ref	
	AdC	125	0.48 (0.32-0.72)	<0.001	0.52 (0.32-0.82)	0.005
	SCC	14	0.48 (0.23-0.97)	0.04	0.6 (0.27-1.34)	0.21
	Glioma	24	0.62 (0.36-1.06)	0.08	0.92 (0.27-3.17)	0.9
Primary site	Other[b]	63	Ref		Ref	
	Breast	26	0.60 (0.37-0.99)	0.04	1.24 (0.69-2.23)	0.47
	Lung	30	0.76 (0.47-1.25)	0.29	1.01 (0.59-1.72)	0.98
	Ovaries	27	0.66 (0.40-1.09)	0.10	1.01 (0.58-1.77)	0.98
	Brain	27	0.87 (0.54-1.39)	0.56	0.7 (0.19-2.53)	0.58
	Prostate	23	0.70 (0.41-1.17)	0.17	1.33 (0.7-2.49)	0.38
Time from diagnosis (months)[c]		196	0.99 (0.99-1.00)	0.002	0.99 (0.99-1.00)	0.003
Number of metastatic sites[d]		196	1.14 (1.01-1.29)	0.04	1.18 (1.02-1.38)	0.03
Metastatic sites[e]	Other	131	Ref			
	Liver	65	1.27 (0.92-1.75)	0.14		
	Other	142	Ref			
	Lung	54	1.13 (0.80-1.59)	0.49		
	Other	144	Ref			
	Bone	52	0.92 (0.65-1.29)	0.63		
	Other	106	Ref			
	Distant lymph nodes	90	0.99 (0.73-1.34)	0.92		
ECOG PS	0	92	Ref		Ref	
	1	93	0.96 (0.70-1.31)	0.79	0.82 (0.56-1.2)	0.31
	2	11	2.85 (1.50-5.42)	0.001	1.42 (0.7-2.86)	0.33
Number of prior systemic treatment regimens		196	0.99 (0.92-1.07)	0.85		
Prior high-dose radiotherapy	No	151	Ref			
	Yes	45	1.00 (0.70-1.43)	0.98		
BMI		194	0.97 (0.94-1.00)	0.08		
Smoking status	Never	68	Ref			
	Current/former	106	1.33 (0.95-1.86)	0.10		
Prior or concurrent other cancer	No	160	Ref			
	Yes	36	0.70 (0.46-1.07)	0.10		
Germline variant	None	181	Ref			
	Undetermined	6	1.34 (0.55-3.27)	0.52		
	Present	9	0.62 (0.29-1.32)	0.22		
Number of affected pathways[f]		110	1.04 (0.97-1.12)	0.25		
RTK/RAS pathway	Not affected	74	Ref		Ref	
	Affected	115	1.61 (1.16-2.24)	0.004	1.81 (1.23-2.67)	0.003
PIK3 pathway	Not affected	115	Ref			
	Affected	74	1.17 (0.85-1.61)	0.33		
Cell cycle pathway	Not affected	157	Ref			
	Affected	32	1.29 (0.86-1.93)	0.22		
Myc pathway	Not affected	170	Ref			
	Affected	19	0.85 (0.49-1.47)	0.55		
Hippo pathway	Not affected	107	Ref			
	Affected	82	0.87 (0.64-1.20)	0.40		
Notch pathway	Not affected	112	Ref			
	Affected	77	0.91 (0.66-1.25)	0.55		

Continued

Table 2. Continued

Variable	Stratum	Number	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Nrf2 pathway	Not affected	180	Ref			
	Affected	9	0.76 (0.36-1.63)	0.48		
TGFβ pathway	Not affected	170	Ref			
	Affected	19	1.49 (0.90-2.46)	0.13		
P53 pathway	Not affected	77	Ref			
	Affected	112	1.20 (0.87-1.65)	0.27		
Wnt pathway	Not affected	118	Ref			
	Affected	71	1.07 (0.77-1.47)	0.69		
TMB-H	No	157	Ref			
	Yes	30	1.30 (0.86-1.97)	0.20		

AdC, adenocarcinoma; BMI, body mass index; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; MMR, mismatch repair; NMTB, National Molecular Tumor Board; ref, reference; SCC, squamous-cell carcinoma; TMB-H, tumor mutational burden high (>10 mutations per megabase).
[a]'Other histologies' include neuroendocrine carcinoma, basal cell carcinoma, mesothelioma, carcinosarcoma, atypical meningioma, and transitional cell carcinoma.
[b]'Other primary sites' include female genital tract excluding ovaries, esophagus-stomach, head-and-neck, skin, pancreas, and urinary tract.
[c]Time from first diagnosis of cancer to date of NMTB.
[d]The 31 patients with locally advanced disease are scored 0.
[e]Patients may have more than one metastatic site. Rarer metastatic sites are not shown or tested.
[f]Seven cases excluded: Data not available (four cases), high numbers of variants of low frequencies due to formalin fixation, prior treatment with temozolomide, and biallelic germline MMR gene mutation.

the IMPRESS-Norway.[41] The short median TTF of 3.5 months is very akin to similar outcome measures in other studies of precision medicine in unselected cohorts of end-stage cancer patients.[17] Hence, long-term benefit is achieved in only a minority and improvements are needed before this treatment principle can be considered outside clinical research projects.

In the present cohort, TMB-H was the most common druggable target identified. We used a cut-point of 10 mut/Mb or higher for assigning patients to treatment with ICI,[24] but due to the limited number of patients, we were unable to assess the predictive value of different cut-points. The value of TMB-H as a tissue-agnostic predictor of benefit of ICI is subject to debate. TMB has failed to predict response in several cancer diagnoses, such as breast and prostate cancers and glioma,[42] and the most optimal cut-point has not been determined and may depend on tumor primary site and histology, the presence of other molecular factors,[43] and methodology used.[44]

Although not statistically significant, our findings indicate that patients with locally advanced disease or a solitary metastatic site may benefit the most from precision medicine. Possible explanations are smaller tumor burden increasing the chance of response,[45] a favorable tumor biology reducing risk of resistance,[46] and enhanced representativeness of molecular profiles of biopsies taken from a single site.[47]

Several methodologies including targeted sequencing, WES, and whole genome sequencing (WGS) are in clinical use for the purpose of identifying druggable targets in cancer patients.[17,48] Their strengths and limitations were reviewed by Satam et al.,[49] concluding that WES and WGS are powerful tools for discovery, while targeted sequencing has less exploratory power but is cost-efficient, presents more manageable data for clinicians, and can give much deeper coverage for rare alleles.[49] By WGS or WES, variants that cannot be targeted but may be clinically important codrivers are disclosed, and variants targeted in early-phase clinical studies that are not included in custom panels can be identified. Moreover, germline variants can be directly classified in non-tumoral DNA. In the present study we used WES as we gained experience with this methodology through prior research projects.[50] However, as part of a nationwide introduction of WGS in a range of diagnoses, this methodology is now used for molecular profiling of cancer patients.

Resistance to treatment is a major obstacle for precision medicine, especially in end-stage cancer as indicated by short time on treatment, PFS, or similar measures.[31,51,11,41] Treatments directed toward evolving molecular resistance mechanisms[52,53] or involving both specific and non-specific drugs[48] are under investigation. An important resistance mechanism is thought to be mediated by parallel, undrugged oncogenic signaling pathways[54] leading to investigations of combinations of drugs targeting several molecular pathways simultaneously.[52,53,32] Clinical evidence for the importance of this mechanism of resistance was presented recently by investigators of the DRUP-trial, who found that affection of more than three oncogenic signaling pathways in tumors was associated with worse outcome in patients treated with drugs targeted against a single pathway.[54] In the present study, more than three pathways were affected in a high fraction (42%) of tumors, but the limited number of patients receiving treatment against a single pathway did not allow for stratified analysis.

Precision medicine programs in end-stage cancer patients are severely hampered by ineligibility of the majority,[25] including failure to obtain a sufficient molecular analysis.[55] However, with the emerging possibility of molecular profiling using alternatives to histological biopsies[56] and an increasing number of targets being druggable, the overall benefit of precision medicine will rise. In this study of a per-protocol population, the fraction of patients initiating targeted treatment almost tripled during the 3-year inclusion

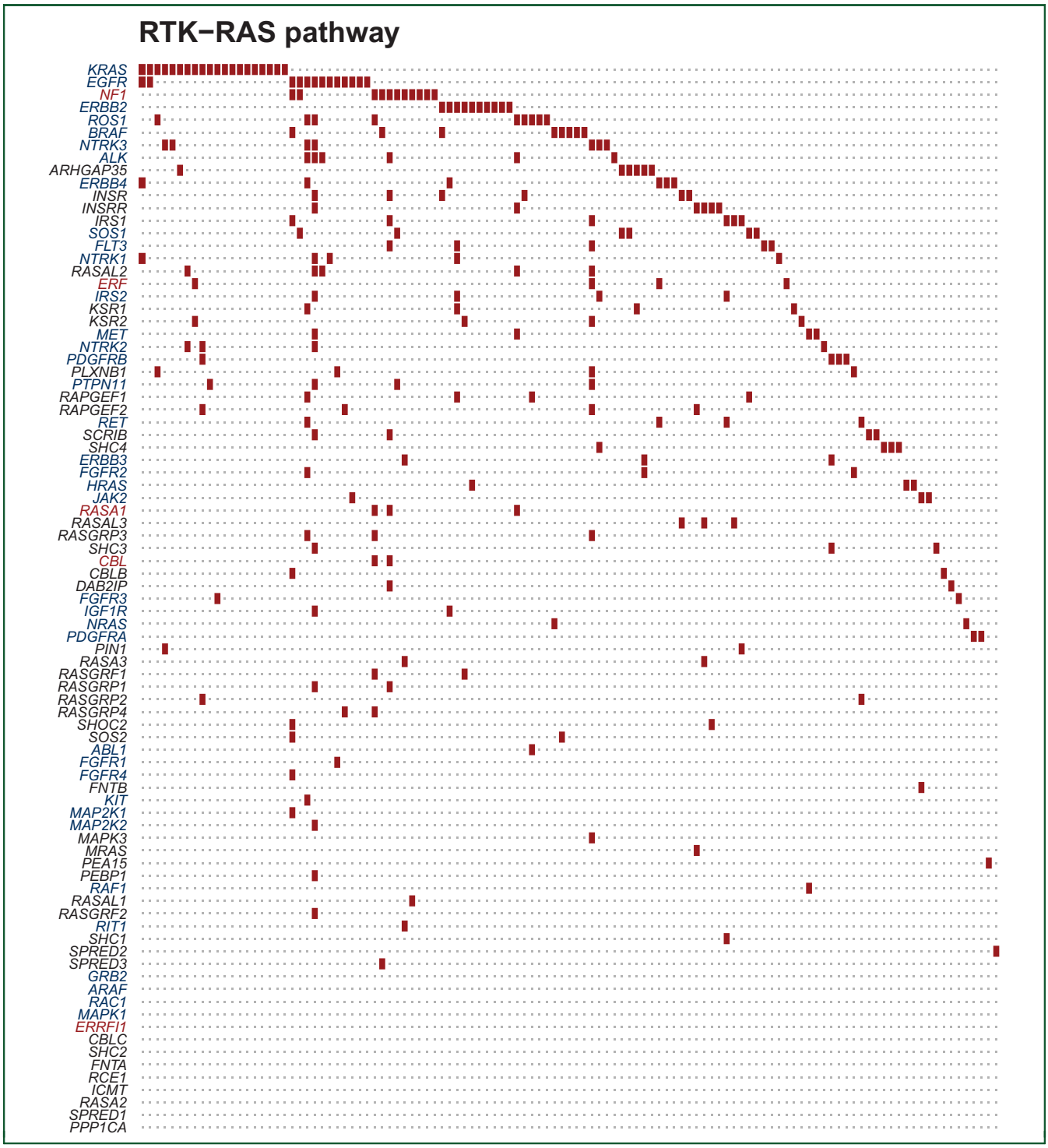

Figure 3. Map of genes affected in the RTK/RAS oncogenic pathway in 115 patients. Each row represents a gene in the RKT/RAS pathway, and each column shows individual mutations in the pathway. Tumor suppressor genes are indicated in red, and oncogenes are indicated in blue.

period, likely reflecting increased access to treatment.[24] In addition, implementing prognostic metrics for patient selection could yield mutual benefits; moreover, enrichment of patients with a greater chance of harboring a druggable target can improve cost-benefit.[25] Future improvements may be achieved by incorporating all these aspects and more into clinical decision tools, e.g. using artificial intelligence.[57]

We found that druggable alterations were enriched in patients with lung cancer in line with ESMO guidelines recommending extended profiling of patients with non-squamous non-small-cell lung cancer.[58] Also, our findings indicated that patients with a single metastatic site may obtain greater benefit from targeted treatment, including improved prognosis. The chance of receiving treatment, if a druggable variant was found, tended to be increased in

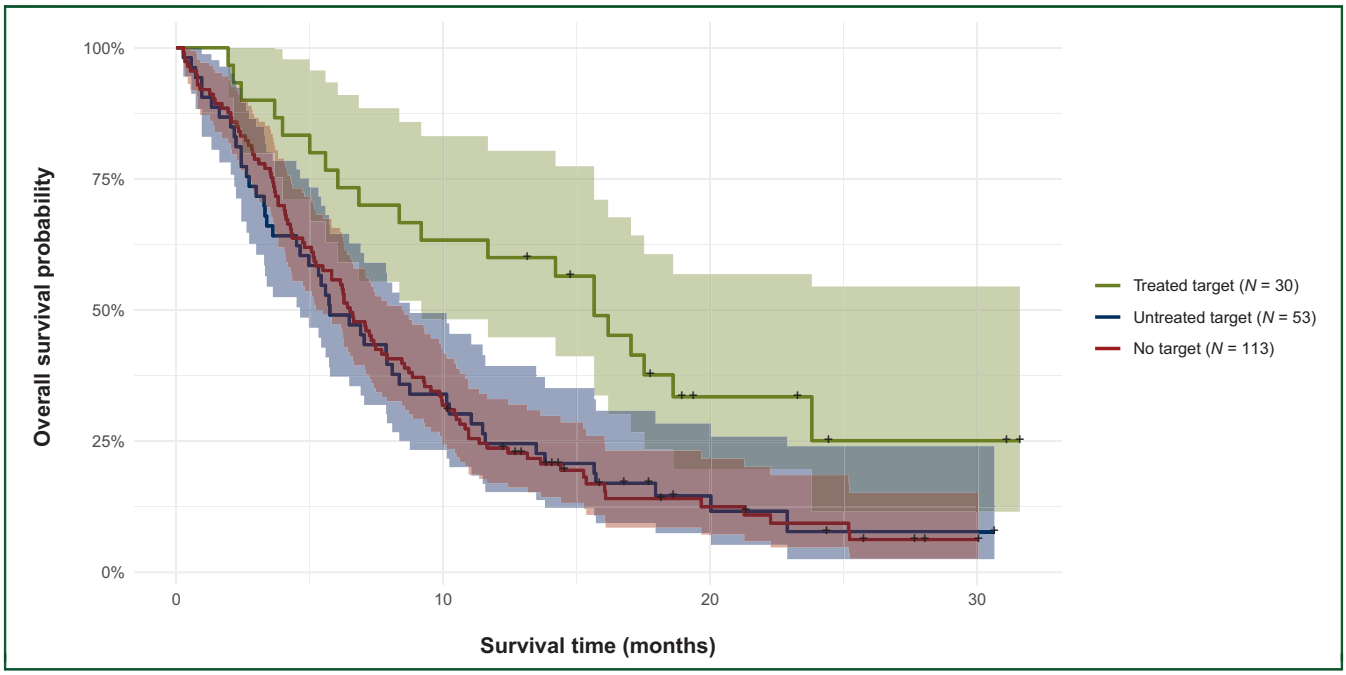

Figure 4. Overall survival of the per-protocol population of end-stage cancer patients according to groups with no druggable target present, druggable target present but untreated, and druggable target present and treated ($P = 0.003$). Index date is date of the National Molecular Tumor Board. Patients alive at the day of last follow-up are censored as indicated by +.

patients in good ECOG PS, and indeed, the major reason for not receiving treatment was deteriorating performance status or early death, which indicates that more patients may benefit if assessment is done earlier. Patients were mostly heavily pretreated, and 60% of patients with a potentially druggable mutation that was not treated by a matched targeted agent did not receive further lines of treatment.

The limitations of this study are mainly the heterogeneity of patients, tumors and treatments, and the non-randomized design, which are common to most similar studies.[59] The definition of a target being 'druggable' was largely subjective being based on clinical and genomic information and available treatments in the country as determined by consensus at the NMTB. A reclassification of treatment 'druggability' according to ESCAT showed that two-thirds were highly druggable (tier 1) but, in contrast to others,[60,61] ESCAT classes had no prognostic impact in our small cohort. The study was not intention-to-treat as we chose to focus on outcome of patients, who had their molecular profile evaluated at the national tumor board. Although patients were not randomized and selection favoring an indolent biology, less comorbidity, and favorable socioeconomic factors in those with a treated druggable target cannot be excluded,[62] the similar baseline clinical characteristics of patients with an untreated and a treated target, as well as the similar survival of patients with an untreated target and no druggable target support a real survival benefit of treatment. Adding to this, the recently reported, randomized phase II ROME trial met its primary endpoint of improved overall response rate and showed an improvement in PFS in patients treated with targeted agents compared with standard of care. OS benefit was not demonstrated, possibly due to cross-over.[63] Similar to our findings, most patients were unable to receive targeted treatment and median PFS was short, indicating that much work has to be done.

In conclusion, in this single-center prospective study a potentially druggable molecular alteration could be found by WES and RNASeq in 42% of cancer patients resistant to standard therapy. The fraction of patients receiving targeted treatment tripled to 22% during the 3-year inclusion period. Although 42% had simultaneous affections of more than three oncogenic pathways, 45% of those treated obtained clinical benefit from targeted treatment. Together with a median OS of 15.7 months for patients treated with targeted drugs, 2.6 times the median OS of patients not treated with such drugs, these results are encouraging and underline the potential benefits of precision medicine even in late-stage cancer patients.

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DISCLOSURE

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